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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,807	10/01/2001	Reuben Matalon	SHUTT-I C1	3645
23599	7590	04/20/2006	EXAMINER	
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			NOAKES, SUZANNE MARIE	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/965,807

Applicant(s)

MATALON ET AL.

Examiner

Suzanne M. Noakes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22, 24, 67-75, 89, 90 and 92-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 67-75, 89, 90 and 92-94 is/are rejected.
- 7) ☒ Claim(s) 22 and 24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims

1. Claims 22, 24, 67-75, 89-90 and 92-94 are pending and under examination in this application. The amendments to the claims filed 26 January 2006 are acknowledged and entered.

Withdrawal of Rejections/Objections

2. Claims 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of amendments to claims.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 68, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The details of the rejection can be found in Section 7 of the previous Office action.

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5. Claims 68, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The details of the rejection can be found in Section 8 of the previous Office action.

6. Claim 92 is rejected under 35 U.S.C. 112, first paragraph, scope of enablement. The details of the rejection can be found in Section 9 of the previous Office action.

Claim Rejections - 35 USC § 102

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 67, 69-75, 89, 90,92 rejected under 35 U.S.C. 102(b) as being anticipated by Matalon et al. (J. Inher. Dis., 1989, 12, 329-331 – Cited on the IDS of 5-18-2005). Matalon et al. teach that they have isolated and purified human aspartoacylase. Further, details of the rejection can be found in Section 10 of the previous Office action.

Response to Arguments

9. Applicant's arguments filed 26 January 2006 have been fully considered but they are not persuasive.

Rejections under 35 USC § 112 1st paragraph

10. Claims 68, 93 and 94 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and with the enablement requirement. The claims are drawn to immunologically active fragments of an isolated human aspartoacylase of SEQ ID No: 2, however, the examiner deemed that Applicants

were not in possession of the fragments of SEQ ID No: 2 that are immunologically active at the time of filing; and that the claims were not enabled because a skilled artisan would be required to figure out which fragments were immunologically active, which was deemed as an undue experimentation because the determination of the immunological epitopes is non-trivial at best.

Applicants argue that the full-length sequences disclosed in the specification inherently discloses fragments and therefore provide a written description of the claimed invention. Furthermore, the citing of *See Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) is not analogous to the present situation because the present application discloses the isolating and complete sequence of a number of different full-length sequences for human aspartoacylase, and therefore does not possess the defect alleged to be present in the Fiers specification. It is also argued that the specification provides a number of specific examples of polypeptide fragments, including SEQ ID No: 10-16 and 24-27. Additionally, the specification also describes amino acid motifs involved in enzyme catalysis, for example, those which are capable of hydrolyzing N-acetyl aspartic acid to aspartate and acetate. Thus, Applicants were clearly in possession of the claimed invention at the time of filing.

The examiner respectfully disagrees. Applicants clearly have disclosed several species of a claimed genus; that is, several fragments of aspartoacylase which do possess activity. However, this is not at all representative of the many combinations of potential immunological fragments. Furthermore, the predictability as to which fragments may or may not possess the immunological activity desired is a significant

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factor in this case. “[I]n some unpredictable areas of chemistry and biology, there is no conception until the invention has been reduced to practice.” *MacMillan v. Moffett*, 432 F.2d 1237, 1234-40, 167 USPQ 550, 552-553 (CCPA 1970). See also *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001) (conception simultaneous with reduction to practice where appellant lacked reasonable certainty that yeast's performance of certain intracellular processes would result in the claimed antigen particles). Thus, while Applicants can provide an idea of what residues they think *may* be required for enzymatic activity, the intricacy of the structure-function relationship of proteins and peptides makes it a less than exact science at best and the details of which areas of the protein are essential for provide the epitopes for immunological activity is extremely tenuous. Hence, while Applicants clearly possess some species of the claimed genus, which does establish they were in possession of these exact sequences with aspartoacylase activity, they have not established that they were in possession of the entire genus of all immunological fragments at the time of filing.

Applicants also argue that the claims are fully enabled for the full scope of the claimed invention because the specification clearly describes assays for which a skilled artisan can use to test the fragments to see if they are biologically and/or immunologically active. However, the enablement requirement is clearly predicated on the fact that an invention must not impose undue experimentation in order practice it, no matter how easy this experimentation may be. In the instant case, a skilled artisan will necessarily be burdened with having to figure out the activities themselves and the predictability in doing so is not guaranteed. Thus, while there is general guidance

provided regarding how to make and test these fragments, the scope of patent protection sought by Applicant as defined by the claims fails to reasonably correlate with the scope of enabling disclosure set forth in the specification.

11. Claim 92 was rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human aspartoacylase that has an altered ability to hydrolyze N-acetyl-aspartic acid where the altered ability is derived from amino acid substitutions at positions 285, 231 or 305 of SEQ ID No: 2, does not reasonably provide enablement for all enzymes that are 95% identical to SEQ ID No: 2 that have altered abilities to hydrolyze N-acetyl-aspartic acid.

Applicants argue that they provide at least three different examples of naturally-occurring mutant alleles, including those recited in claim 22 and that other mutations can be isolated without undue experimentation. At least seven different methods are disclosed in the specification for identifying mutations in patient samples and several conserved regions are also disclosed. Thus, it is reasoned that skilled artisan will be able to understand how to carry out the claimed invention without undue experimentation.

The examiner respectfully disagrees. Applicants assert that they have disclosed amino acid positions 18-24, 275-278 and 293[sic]-289 which are all conserved sequences and that "The specification describes several conserved regions that, when mutated, result in altered enzyme activity." However, this may or may not be the case. The conserved regions according to the specification are for VXEXXXY motif (the aspartoacylase sequence is VNEAAYY, see p. 9 1st paragraph). However, noting that

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the motif has several X's and that these X's represent any amino acid, then does this mean that a skilled artisan can substitute any of these X amino acids and obtain an altered activity? Maybe, maybe not. Clearly the essential amino acids, V, E and Y may be required, but substitution of any of the X's are an unknown quantity. Likewise, as skilled artisans also recognize, the three-dimensional active site is full of essential bonds/contacts such as hydrogen bonds and salt-bridges that also may be necessary for proper activity and there is absolutely no way to predict these interactions based a linear sequence. The only way to determine this is through structural analysis via protein crystallography or nuclear magnetic resonance. Thus, while a consensus sequence might give a some indication of what is essential for activity, it by no means gives a predictable and complete analysis. Thus, it is reasoned that undue experimentation would be expected and necessary for a skilled artisan to practice the claimed invention.

Rejections under 35 USC § 102(b)

12. Claims 67, 69-75, 89, 90 and 92 were rejected under 35 U.S.C. 102(b) as being anticipated by Matalon et al. (J. Inher. Dis., 1989, 12, 329-331 – Cited on the IDS of 5-18-2005) because Matalon et al. teach that they have isolated and purified human aspartoacylase. Specifically, cells from patients were cultivated in Matalon's modified Eagle's medium (p. 329, last paragraph), and that aspartoacylase was purified to homogeneity from human (and bovine) brain. Furthermore, based upon SDS-gel

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electrophoresis, the molecular weight was determined to be 58 kDa (this was reported as unpublished results).

Applicants traverse this rejection for several reasons. First, it is suggested that the prior art reference is not enabling. That is, while it is disclosed that Matalon et al. have purified human aspartoacylase, the reference is not enabling because there is no purification protocol describing how said protein was actually purified. Furthermore, Matalon et al. do not describe recombinant and purified human aspartoacylase (as recited in claim 67) or a human aspartoacylase recombinantly produced in a host cell (claims 74, 75, 89 and 90). It is suggested that these limitations do breath life and meaning into the claims and they cannot be overlooked.

The examiner respectfully disagrees with Applicant on both arguments. While it is true that there is no specific purification protocol in the Matalon et al. reference, the knowledge and skills possessed by one skilled in the art would be sufficient to develop a purification protocol. In fact the MPEP [2121.01] even states that, a reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). Thus a skilled artisan could easily call on his/her own knowledge of the art and if necessary utilize the general purification guides available, if needed, to devise a scheme and protocol for the purification of human aspartoacylase. Such references as Methods in Enzymology, 1990, Vol. 182, pp. 1-894: Guide to Protein

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Purification, has 66 different articles addressing nearly every need for a skilled artisan to devise their purification protocols. Hence, a skilled artisan could indeed combine his or her own knowledge and make the claimed invention.

In regards to the argument that a recombinant protein is different than naturally occurring one and these limitations are crucial and do give meaning to the claims, the examiner respectfully disagrees. If a skilled artisan were to purify human aspartoacylase, from the natural source, and also from a recombinant source, obtain an equally purified protein, place each purified protein in two separately non-labeled test tubes and mix them up so as to not know which protein came from which source, there would be almost no way to ultimately distinguish the two proteins from each other. Whether aspartoacylase is produced recombinantly or isolated from its natural source, the end result is the same, its *still* aspartoacylase. It is further argued that claim 71 distinguishes over Matalon et al. because the claims expressly states that the aspartoacylase is "free from other human proteins". When purifying a protein it is most desirable to purify to homogeneity, that is, where the protein of interest is free from *all* other proteins, regardless of its source. This certainly is within the skill and knowledge of a skilled artisan, and again, references such as the Methods in Enzymology reference cited above. In fact, the first two lines of the entire book states: ""Don't waste clean thinking on dirty enzymes, is an admonition of Efraim Racker's which is at the core of enzymology and good chemical practice. It says simply that detailed studies of how an enzyme catalyzes the conversion of one substance to another is generally a

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waste of time until the enzyme has been purified away from the other enzymes and substances that make up a crude cell extract.” (see Chapter 1, page 1, 1st two lines).

The final argument by Applicants is that Matalon et al. do not disclose human aspartoacylase which be suitable as a pharmaceutical preparation (e.g. claim 69) and that the preparation of Matalon et al., *could* be contaminated with extraneous human proteins, viruses and bacteria. Likewise claim 72 would also be patentable over Matalon et al. for these same reasons.

The examiner disagrees and believes it is within the knowledge of any skilled artisan to recognize that it is essential to remove all excess proteins as cited above, and place the protein in a suitable buffer solution at the conclusion of the purification protocol to maintain the enzymes stability and also remove any harsh buffers from the purification. Thus, the last step in most any given protein purification protocol is to dialyze the protein or enzyme into a friendly neutral buffer. Thus, it is deemed that these claim limitations do differentiate the protein as taught by Matalon et al.

Allowable Subject Matter

13. Claims 22 and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. In a phone call to Mr. Richard Lebovitz on 5 April 2006, the examiner indicated that claims 22 and 24 were allowable, however, the rest of the claims were not.

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Applicants elected to receive on Office action on the merits rather than an Allowance for claims 22 and 24.

Conclusion

15. Claims 67-75,89,90 and 92-94 are rejected. Claims 22 and 24 are objected to.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

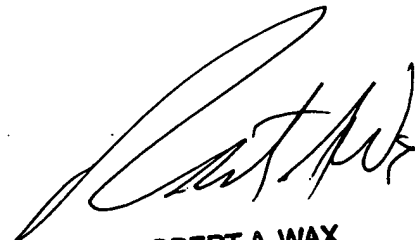
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16 April 2006


ROBERT A. WAX
PRIMARY EXAMINER